

Glass

WHAT IS CLAIMED IS:

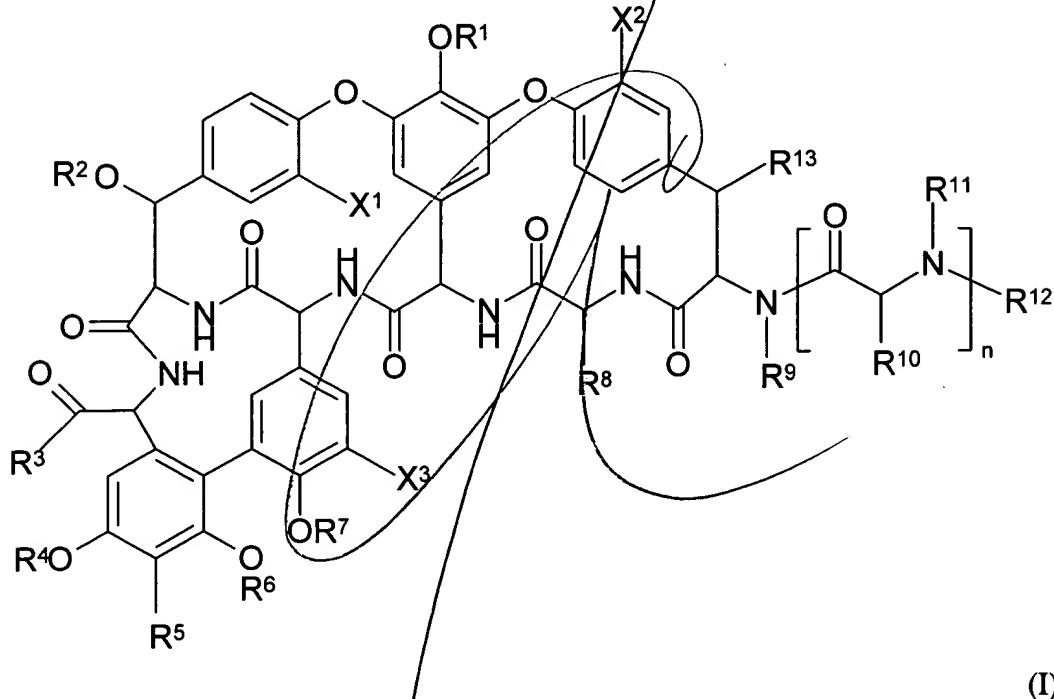
1. A composition comprising a cyclodextrin and a glycopeptide antibiotic, or a pharmaceutically acceptable salt thereof.
2. The composition of claim 1 which further comprises water.
3. The composition of claim 1 which is a powder.
4. The composition of claim 1 which is a lyophilized powder.
5. A pharmaceutical composition comprising an aqueous cyclodextrin carrier and a therapeutically effective amount of a glycopeptide antibiotic, or a pharmaceutically acceptable salt thereof.
6. The pharmaceutical composition of Claim 5, wherein the pharmaceutical composition comprises:
 - (a) a therapeutically effective amount of a glycopeptide antibiotic, or a pharmaceutically acceptable salt thereof;
 - (b) 1 to 40 weight percent of a cyclodextrin; and
 - (c) 60 to 99 weight percent of water, provided that the components of the composition total 100 weight percent.
7. The pharmaceutical composition of Claim 5, wherein the cyclodextrin is hydroxypropyl- β -cyclodextrin or sulfobutyl ether β -cyclodextrin.
8. The pharmaceutical composition of Claim 7, wherein the cyclodextrin is hydroxypropyl- β -cyclodextrin.

9. The pharmaceutical composition of Claim 6, wherein the cyclodextrin comprises about 5 to 35 weight percent of the composition.

10. The pharmaceutical composition of Claim 9, wherein the cyclodextrin comprises about 10 to 30 weight percent of the composition.

11. The pharmaceutical composition of Claim 6, wherein the glycopeptide antibiotic is a lipidated glycopeptide antibiotic.

12. The pharmaceutical composition of Claim 1, wherein the glycopeptide antibiotic is a compound of formula I:



wherein:

R¹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and

-R^a-Y-R^b-(Z)_x; or R¹ is a saccharide group optionally substituted with -R^a-Y-R^b-(Z)_x, R^f, -C(O)R^f, or -C(O)-R^a-Y-R^b-(Z)_x;

R² is hydrogen or a saccharide group optionally substituted with -R^a-Y-R^b-(Z)_x, R^f, -C(O)R^f, or -C(O)-R^a-Y-R^b-(Z)_x;

R³ is -OR^c, -NR^cR^c, -O-R^a-Y-R^b-(Z)_x, -NR^c-R^a-Y-R^b-(Z)_x, -NR^cR^e, or -O-R^e; or R³ is a nitrogen-linked, oxygen-linked, or sulfur-linked substituent that comprises one or more phosphono groups;

R⁴ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, -R^a-Y-R^b-(Z)_x, -C(O)R^d and a saccharide group optionally substituted with -R^a-Y-R^b-(Z)_x, R^f, -C(O)R^f, or -C(O)-R^a-Y-R^b-(Z)_x;

R⁵ is selected from the group consisting of hydrogen, halo, -CH(R^c)-NR^cR^c, -CH(R^c)-NR^cR^e, -CH(R^c)-NR^c-R^a-Y-R^b-(Z)_x, -CH(R^c)-R^x, -CH(R^c)-NR^c-R^a-C(=O)-R^x, and a substituent that comprises one or more phosphono groups;

R⁶ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, -R^a-Y-R^b-(Z)_x, -C(O)R^d and a saccharide group optionally substituted with -NR^c-R^a-Y-R^b-(Z)_x, or R⁵ and R⁶ can be joined, together with the atoms to which they are attached, form a heterocyclic ring optionally substituted with -NR^c-R^a-Y-R^b-(Z)_x;

R⁷ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, -R^a-Y-R^b-(Z)_x, and -C(O)R^d;

R⁸ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R⁹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R¹⁰ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; or R⁸ and R¹⁰ are joined to form -Ar¹-O-Ar²-, where Ar¹ and Ar² are independently arylene or heteroarylene;

R¹¹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic, or R¹⁰ and R¹¹ are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring;

R¹² is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, -C(O)R^d, -C(NH)R^d, -C(O)NR^cR^c, -C(O)OR^d, -C(NH)NR^cR^c and -R^a-Y-R^b-(Z)_x, or R¹¹ and R¹² are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring;

R¹³ is selected from the group consisting of hydrogen or -OR¹⁴;

R¹⁴ is selected from hydrogen, -C(O)R^d and a saccharide group;

each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene, provided R^b is not a covalent bond when Z is hydrogen;

each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and -C(O)R^d;

each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^e is a saccharide group;

each R^f is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, or heterocyclic;

R^x is an N-linked amino saccharide or an N-linked heterocycle;

X^1 , X^2 and X^3 are independently selected from hydrogen or chloro;

each Y is independently selected from the group consisting of oxygen, sulfur, $-S-S-$, $-NR^c-$, $-S(O)-$, $-SO_2-$, $-NR^cC(O)-$, $-OSO_2-$, $-OC(O)-$, $-NR^cSO_2-$, $-C(O)NR^c-$, $-C(O)O-$, $-SO_2NR^c-$, $-SO_2O-$, $-P(O)(OR^c)O-$, $-P(O)(OR^c)NR^c-$, $-OP(O)(OR^c)O-$, $-OP(O)(OR^c)NR^c-$, $-OC(O)O-$, $-NR^cC(O)O-$, $-NR^cC(O)NR^c-$, $-OC(O)NR^c-$, $-C(=O)-$, and $-NR^cSO_2NR^c-$;

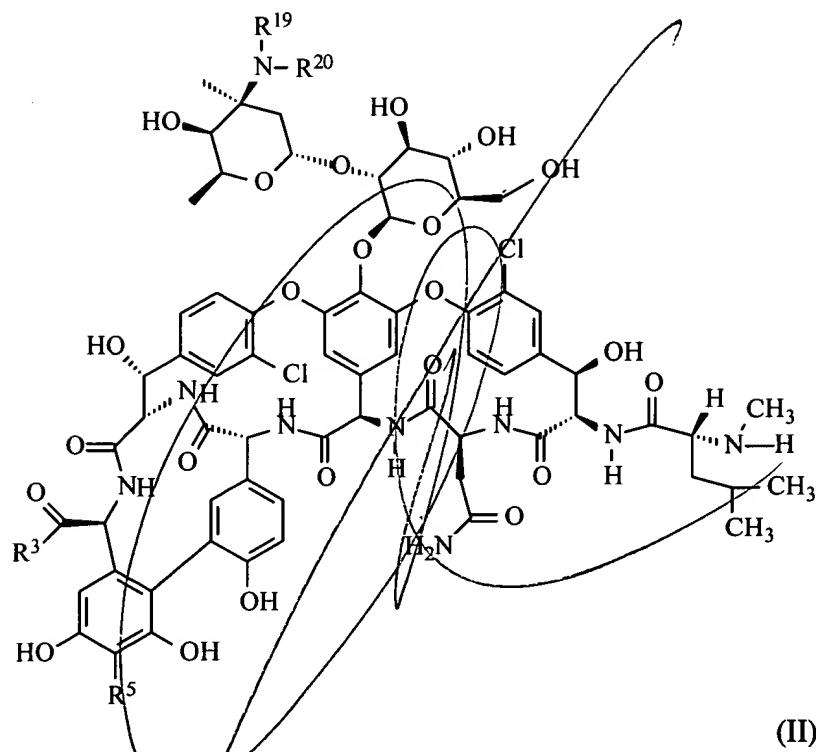
each Z is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic;

n is 0, 1 or 2; and

x is 1 or 2;

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

13. The pharmaceutical composition of Claim 1, wherein the glycopeptide antibiotic has formula II:



wherein:

R^{19} is hydrogen;

R^{20} is $-R^a-Y-R^b-(Z)_x$, R^f , $-C(O)R^f$, or $-C(O)-R^a-Y-R^b-(Z)_x$; and

R^a , Y , R^b , Z , x , R^f , R^3 , and R^5 are as defined in Claim 7;

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

14. A method of treating a mammal having a bacterial disease, the method comprising administering to the mammal a pharmaceutical composition of claim 1.

15. A method of treating a bacterial disease in a mammal, the method comprising administering to the mammal a therapeutically effective amount of a glycopeptide antibiotic in combination with a cyclodextrin.

16. A method for reducing tissue accumulation of a glycopeptide antibiotic when administered to a mammal, the method comprising administering the glycopeptide antibiotic to the mammal in a pharmaceutical composition comprising a cyclodextrin and a therapeutically effective amount of the glycopeptide antibiotic or a pharmaceutically acceptable salt thereof.

17. A method for reducing nephrotoxicity produced by a glycopeptide antibiotic when administered to a mammal, the method comprising administering the glycopeptide antibiotic to the mammal in a pharmaceutical composition comprising a cyclodextrin and a therapeutically effective amount of the glycopeptide antibiotic or a pharmaceutically acceptable salt thereof.

18. A method for reducing histamine release produced by a glycopeptide antibiotic when administered to a mammal, the method comprising administering the glycopeptide antibiotic to the mammal in a pharmaceutical composition comprising a cyclodextrin and a therapeutically effective amount of the glycopeptide antibiotic or a pharmaceutically acceptable salt thereof.

19. A method for reducing vascular irritation produced by a glycopeptide antibiotic when administered to a mammal, the method comprising administering the glycopeptide antibiotic to the mammal in a pharmaceutical composition comprising a cyclodextrin and a therapeutically effective amount of the glycopeptide antibiotic or a pharmaceutically acceptable salt thereof.